Protein Intake and Risk of Renal Cell Cancer

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Background: **Renal cell cancer, although still relatively uncommon, has been increasing in incidence in the United States and other countries around the world.** ***Purpose:*** **Since previous studies have suggested an association with high intake of meat, we sought to further examine the role of diet in renal cell cancer risk.** ***Methods:*** **Patients with histologically confirmed renal cell cancer that had been diagnosed between July 1, 1988, and December 31, 1990, were identified through the Minnesota Cancer Surveillance System, a statewide cancer registry. The patients eligible for inclusion in this study were white residents of Minnesota between 20 and 79 years of age. Control subjects were selected from the general population of Minnesota residents; subjects under age 65 were selected by use of a random-digit-dialing method and those 65 years or older were sampled from the Health Care Financing Administration files. Population-based control subjects were frequency-matched to cases by sex and 5-year age groups. A total of 690 patients and 707 control subjects were interviewed. Patients and control subjects were similar in distribution by sex, age, and educational level. Usual adult dietary intakes were assessed by questionnaire, and odds ratios were calculated by logistic regression analyses.** ***Results:*** **Significantly increased risks of renal cell cancer were observed with increasing consumption of several food groups, including red meat (*P* for trend = .05), high-protein foods (*P* = .01), and staple (grains, breads, and potatoes) foods (*P* = .009). When examined by macronutrient status, risks increased monotonically with the amount of protein intake, from 1.2 (95% confidence interval [CI] = 0.7-1.9) to 1.4 (95% CI = 0.8-2.5) and 1.9 (95% CI = 1.0-3.6) (*P* for trend = .03) in the second, third, and fourth quartiles of intake, respectively, after adjustment for age, sex, caloric intake, body mass index, and cigarette smoking. No significant or consistent associations were detected with the intake of other dietary nutrients or beverages.** ***Conclusion:*** **Although an independent effect of dietary protein has not been previously associated with renal cell cancer, high protein consumption has been related to development of other chronic renal conditions that may predispose an individual to this cancer.** ***Implication:*** **These findings should prompt further study of dietary protein and its potential contribution to the origins of renal cell cancer. [J Natl Cancer Inst 86:1131-1139, 1994]**

Malignant tumors of the kidney rank about 12th in cancer incidence and mortality in the United States (*1*). It is estimated that more than 27 600 new cases will be diagnosed and nearly 11 300 persons in the United States will die of these tumors (kidney and other urinary, except bladder; most are renal cell cancers) in 1994 (*1*). Since 1970, age-adjusted incidence rates for renal cell cancer (adenocarcinomas of the renal parenchyma, the primary tumor in the adult kidney) have risen about 2% per year in each of the four major race/sex groups (*2*). Incidence rates are generally higher in western countries than in Asia or Latin America, although recently rates have been increasing in all areas of the world (*3*).

Except for cigarette smoking and excess body weight, risk factors for renal cell cancer are poorly understood. There are reports that certain occupational exposures, use of diuretic drugs, history of kidney diseases, dietary habits, and other factors are related to risk, but the evidence is still inconclusive (*4*). Correlation studies have reported an association between kidney cancer mortality and per-capita consumption of protein and fat (*5,6*), and a few case–control studies have reported a link with increased meat intake (*4*).

In this population-based, case–control study, one of the largest to date, we sought to identify dietary risk factors for renal cell cancer in Minnesota, a state with relatively high incidence and mortality rates (*7,8*).

Methods

Patients with histologically confirmed renal cell cancer (International Classification of Diseases, 9th revision, code 189.0) that was newly diagnosed between July 1, 1988, and December 31, 1990, were identified through the Minnesota Cancer Surveillance System, a statewide cancer registry (*9*). Patients were white residents of Minnesota, between 20 and 79 years of age. Of the 796 eligible patients, written informed consents and interviews were obtained for 690 (87%), including 241 interviews with next of kin of patients who died or were too ill to be interviewed.

Population-based control subjects were frequency matched to cases by sex and 5-year age groups. Minnesota residents under age 65 were selected by use of a random-digit-dialing method (*10*), and those 65 years of age or older were sampled from the files of the Health Care Financing Administration (*11*). For random-digit-dialing control subjects, the overall interview response rate was

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See "Note" section following "References."

84%, which was a product of a 93% response rate at the household-screening phase and a 90% response rate at the interview phase. For the Health Care Financing Administration control subjects, the interview response rate was 87%. A total of 707 control subjects were interviewed.

In-person, structured interviews were conducted in the homes of the study subjects by trained interviewers to elicit information on demographic characteristics, lifetime use of tobacco and alcohol; history of height, weight, and selected medical conditions; use of analgesics and prescription diuretics; and occupational history. To the extent possible, precautions were taken to blind the interviewers with regard to the case–control status of the subjects. At the end of the interview, the respondents were given a self-administered food-frequency questionnaire (*12*), which sought usual adult dietary practices prior to 1987, to be completed later and returned by mail. The returned diet questionnaires were edited, and items left unanswered or requiring clarification were retrieved in a follow-up telephone call by the interviewer.

Of the subjects interviewed for the study, 632 patients (79% of 796 eligible patients) and 653 control subjects (79% of 707 eligible control subjects) returned the diet questionnaire. A number of subjects, whose responses were considered unreliable, were excluded from the analysis, including 48 patients (47 with data provided by next of kin) and three control subjects who had seven or more skipped food items or had questionable data and 50 patients whose next-of-kin respondent was not a spouse. Also excluded were two patients with unknown smoking status, since smoking is a risk factor and should be adjusted for in analysis of dietary intake. The final analysis included 532 patients (67% of eligible patients) and 650 control subjects (79% of eligible control subjects). Among the patients, 415 (78%) were directly interviewed and 117 (22%) had a spouse providing the dietary information (henceforth referred to as next-of-kin case subjects).

The diet questionnaire included the frequency and portion size of 65 food items, selected restaurant foods and fast foods, types of fat usually used, degree of "doneness" and the method of cooking red meat, and the use of supplemental vitamins and minerals. For analysis, frequency of intake of 14 food groups was examined (*see* Appendix Table 1 for a listing of the food groups and the items in these groups). A decision was made to set the value of missing food items to zero (never eaten or eaten less than once per month), since these foods tended to be consumed infrequently (e.g., collard greens and liver). For next-of-kin case subjects whose spouses reported consumption of a specific food item but the frequency of intake was unknown, the intake was imputed using the median values of next-of-kin case subjects who consumed the food item, separately for men and women. Of the 1182 subjects included in the analysis, 82 (6.9%) had one missing item, 20 (1.7%) had two, and 12 (1.0%) had three to six.

Computation of dietary nutrient intakes was based on the Block database (*13*), which used information derived from the Second National Health and Nutrition Examination Survey (NHANES II) (*14*) and nutrient values from the U.S. Department of Agriculture food consumption data (*15*). Total dietary intake of each nutrient was calculated by summing the amount of intake from all food items, which were individually estimated by multiplying the nutrient content to the reported portion size and the frequency of intake for each item.

Consumption of foods and nutrients was divided into quartiles, based on the distributions among control subjects, separately for men and women, with approximately equal numbers of control subjects in each intake stratum (*see* Appendix Table 2 for cutpoints for food group quartiles and Appendix Table 3 for nutrient quartiles). Stratified analysis was used initially to examine the data. Logistic regression models were used to examine multivariate relationships, and 95% confidence intervals (CIs) of the relative risk estimates were computed (*16*). Potential confounding effects of risk factors previously linked to renal cell cancer, such as smoking status, body mass index (BMI), a history of kidney diseases and hypertension, and use of diuretics or antihypertensive drugs were evaluated and adjusted for, if necessary. Nutrient results are presented with and without adjustment for caloric intake. Caloric adjustment procedures included standard and energy-partition methods (*17*). Chi-square tests for linear trend (one sided) were calculated as necessary (*18*). Results for men and women were combined, since similar findings were observed for both sexes. Because frequency of intake of some food items may not be reported accurately by next-of-kin respondents (*19*), risk estimates were based only on information from directly interviewed case patients and control subjects, while information from next-of-kin case subjects was examined separately and only to evaluate the consistency of associations in the study.

Results

Directly interviewed patients and control subjects were similar in distribution by sex (62% male patients and 67% male control subjects), age (34% patients and 36% control subjects under age 59 and 29% patients and 31% control subjects over age 69), and educational level (25% patients and 25% control subjects did not graduate from high school, and 31% patients and 34% control subjects had some education at the college level). While the educational levels of next-of-kin case subjects and control subjects were comparable, next-of-kin case subjects were more likely than control subjects to be male (79%) and older (74% aged 59 or older).

Table 1 shows that after adjustment for age, sex, cigarette smoking (nonsmoker, former smoker, and current smoker), and quartile of BMI, renal cell cancer among direct respondents was positively associated with consumption of red meat (P for trend = .05), staple foods (P = .009), and high-protein foods (P = .01). Similar food-group results were observed for next-of-kin case subjects (data not shown).

Table 2 shows results for calories, macronutrients, and micronutrients in relation to risk of renal cell cancer. Risk estimates are presented both with and without adjustment for calories. Risk of renal cell cancer increased with the amount of caloric consumption, from 1.0 (95% CI = 0.7-1.6) in the second quartile to 1.6 (95% CI = 1.1-2.3) and 1.8 (95% CI = 1.3-2.6) in the third and fourth quartiles of intake. Adjustment for calories reduced the positive association to near unity for a number of nutrients, including carbohydrates, animal and plant proteins, beta carotene, vitamin E, calcium, and iron. The reversal of the association with fat intake after adjustment for calories is not surprising, given the high correlations between intake of calories and total fat (Pearson correlation coefficient = .95). Correlations between intake of calories and other macronutrients were also strong and may explain the lack of associations, except for total protein, observed for macronutrients after caloric adjustment. The Pearson correlation coefficients between calories and carbohydrate, total protein, animal protein, and plant protein were .93, .90, .81, and .82, respectively.

Risks for total protein intake were largely unaltered by caloric adjustment, increasing monotonically with amount consumed, from 1.2 (95% CI = 0.7-1.9) in the second quartile to 1.4 (95% CI = 0.8-2.5) and 1.9 (95% CI = 1.0-3.6) in the third and fourth quartiles, respectively (P for trend = .03). When examined by levels of calories (Table 3), risks increased with the amount of protein consumption only for caloric intake above the median (third and fourth quartiles). Because of the small numbers of subjects who consumed a large amount of protein but few calories, or vice versa, a detailed assessment of risks in these extreme levels was not possible. When intake of total protein was cross-classified with total fat intake, a clear pattern of increased risk with increasing protein but not fat intake was seen (Table 4).

To further assess the relationship among the macronutrients that constitute dietary caloric intake, we examined a logistic regression model using the energy-partition method with protein, fat, and carbohydrate. The risks increased with the amount of protein intake (risks for the second, third, and fourth quartiles of

Table 1. ORs and 95% CIs for renal cell cancer in relation to food-group consumption from self-administered questionnaire among Minnesota residents

Food group	Quartiles	No. of direct		OR* (95% CI)
		Case patients	Control subjects	
Red meat	I (low)	85	159	1.0 (—)
	II	98	168	1.1 (0.7-1.5)
	III	111	161	1.2 (0.8-1.7)
	IV (high)	121	162	1.3 (0.9-1.9)
Chicken/fish	I	88	168	1.0 (—)
	II	104	158	1.3 (0.9-1.8)
	III	106	156	1.3 (0.9-1.9)
	IV	117	168	1.3 (0.9-1.9)
Preserved meats	I	98	155	1.0 (—)
	II	100	159	1.0 (0.7-1.4)
	III	102	171	0.9 (0.7-1.3)
	IV	115	165	1.0 (0.7-1.5)
All meats	I	94	161	1.0 (—)
	II	94	161	1.0 (0.7-1.4)
	III	105	167	1.0 (0.7-1.4)
	IV	122	161	1.2 (0.9-1.7)
Dairy products	I	96	162	1.0 (—)
	II	80	162	0.8 (0.6-1.2)
	III	126	164	1.3 (0.9-1.8)
	IV	113	162	1.2 (0.8-1.7)
Citrus fruit/juices	I	105	160	1.0 (—)
	II	109	166	1.1 (0.8-1.5)
	III	107	159	1.1 (0.7-1.5)
	IV	94	165	1.0 (0.7-1.4)
All fruits	I	98	160	1.0 (—)
	II	114	164	1.1 (0.8-1.6)
	III	89	165	0.9 (0.6-1.3)
	IV	114	161	1.2 (0.8-1.7)
Yellow/green vegetables	I	97	150	1.0 (—)
	II	108	177	1.0 (0.7-1.4)
	III	119	162	1.2 (0.8-1.7)
	IV	91	161	0.9 (0.6-1.3)
Cruciferous vegetables	I	96	159	1.0 (—)
	II	102	141	1.2 (0.8-1.7)
	III	124	200	1.0 (0.7-1.5)
	IV	93	150	1.0 (0.7-1.5)
All vegetables	I	106	163	1.0 (—)
	II	82	163	0.8 (0.6-1.1)
	III	118	160	1.1 (0.8-1.6)
	IV	109	164	1.0 (0.7-1.5)
Staple foods	I	80	162	1.0 (—)
	II	98	160	1.3 (0.9-1.9)
	III	115	166	1.4 (1.0-2.1)
	IV	122	162	1.6 (1.1-2.3)
Desserts	I	87	161	1.0 (—)
	II	113	166	1.3 (0.9-1.8)
	III	107	159	1.3 (0.9-1.9)
	IV	108	164	1.3 (0.9-1.8)
High-protein foods	I	77	163	1.0 (—)
	II	98	161	1.3 (0.9-1.8)
	III	106	164	1.3 (0.9-2.0)
	IV	134	162	1.7 (1.2-2.5)
Restaurant/fast foods	I	106	163	1.0 (—)
	II	93	163	0.9 (0.6-1.3)
	III	97	162	0.9 (0.6-1.3)
	IV	119	162	1.1 (0.8-1.6)

*Adjusted for age, sex, cigarette smoking, and BMI.

intake being 1.3 [95% CI = 0.8-2.1], 1.8 [95% CI = 1.0-3.0], and 2.6 [95% CI = 1.4-4.7], respectively) and tended to decrease with total fat intake (risks for the second, third, and fourth quartiles of fat being 0.6 [95% CI = 0.4-1.0], 0.9 [95% CI = 0.5-1.4], and 0.5 [95% CI = 0.3-0.9], respectively). Risks for the corresponding quartiles of carbohydrate intake were 1.1 (95% CI = 0.7-1.6), 1.0 (95% CI = 0.6-1.6), and 1.4 (95% CI = 0.8-2.4), respectively.

High intake of protein from both animal and plant sources appeared to contribute to the risk of renal cell cancer. Cross-classification of animal and plant protein intake, unadjusted for calories, showed excess risks at high levels of consumption of either animal or plant protein (data not shown). After adjustment for age, sex, cigarette smoking, BMI, and plant protein intake, risks for the second, third, and fourth quartiles of animal protein intake were 1.1 (95% CI = 0.7-1.6), 1.4 (95% CI = 0.9-2.1), and

Table 2. ORs and 95% CIs for renal cell cancer in relation to dietary nutrient intake among Minnesota residents

Nutrients	Quartiles	No. of direct		OR* (95% CI)	OR† (95% CI)
		Cases	Controls		
Calories	I (low)	75	161	1.0 (—)	— (—)
	II	77	163	1.0 (0.7-1.6)	— (—)
	III	124	164	1.6 (1.1-2.3)	— (—)
	IV (high)	139	162	1.8 (1.3-2.6)	— (—)
Carbohydrates	I	79	161	1.0 (—)	1.0 (—)
	II	91	163	1.2 (0.8-1.7)	1.0 (0.6-1.6)
	III	101	164	1.2 (0.9-1.8)	0.8 (0.4-1.4)
	IV	144	162	1.8 (1.3-2.6)	1.1 (0.6-2.2)
Total proteins	I	70	161	1.0 (—)	1.0 (—)
	II	84	164	1.2 (0.8-1.7)	1.2 (0.7-1.9)
	III	110	163	1.5 (1.1-2.3)	1.4 (0.8-2.5)
	IV	151	162	2.0 (1.4-2.9)	1.9 (1.0-3.6)
Animal proteins	I	76	161	1.0 (—)	1.0 (—)
	II	87	164	1.1 (0.8-1.6)	1.0 (0.7-1.5)
	III	116	162	1.5 (1.0-2.2)	1.2 (0.7-1.8)
	IV	136	163	1.7 (1.2-2.4)	1.1 (0.7-1.9)
Plant proteins	I	82	162	1.0 (—)	1.0 (—)
	II	89	162	1.1 (0.8-1.6)	0.9 (0.6-1.4)
	III	109	164	1.3 (0.9-1.9)	0.9 (0.6-1.4)
	IV	135	162	1.6 (1.1-2.3)	0.9 (0.5-1.6)
Total fats	I	87	162	1.0 (—)	1.0 (—)
	II	73	162	0.8 (0.6-1.2)	0.6 (0.4-1.0)
	III	136	164	1.5 (1.0-2.1)	0.7 (0.4-1.3)
	IV	119	162	1.3 (0.9-1.8)	0.4 (0.2-0.8)
Saturated fats	I	83	162	1.0 (—)	1.0 (—)
	II	99	164	1.2 (0.8-1.7)	0.9 (0.6-1.4)
	III	109	162	1.3 (0.9-1.9)	0.6 (0.3-1.0)
	IV	124	162	1.4 (1.0-2.0)	0.4 (0.2-0.9)
Beta carotene	I	94	162	1.0 (—)	1.0 (—)
	II	96	162	1.0 (0.7-1.5)	0.9 (0.6-1.3)
	III	118	164	1.2 (0.9-1.8)	1.0 (0.7-1.5)
	IV	107	162	1.1 (0.8-1.6)	0.8 (0.5-1.2)
Vitamin C	I	98	162	1.0 (—)	1.0 (—)
	II	91	162	0.9 (0.8-1.3)	0.8 (0.5-1.1)
	III	121	164	1.2 (0.8-1.7)	0.9 (0.6-1.4)
	IV	105	162	1.1 (0.8-1.6)	0.8 (0.5-1.2)
Vitamin E	I	74	161	1.0 (—)	1.0 (—)
	II	93	163	1.2 (0.8-1.8)	1.0 (0.7-1.6)
	III	121	164	1.5 (1.1-2.2)	1.1 (0.7-1.8)
	IV	127	162	1.6 (1.1-2.4)	1.0 (0.6-1.8)
Calcium	I	84	162	1.0 (—)	1.0 (—)
	II	90	162	1.1 (0.8-1.6)	1.0 (0.7-1.4)
	III	107	164	1.3 (0.9-1.8)	1.0 (0.6-1.5)
	IV	134	162	1.5 (1.1-2.2)	1.0 (0.7-1.6)
Iron	I	72	161	1.0 (—)	1.0 (—)
	II	101	167	1.4 (0.9-2.0)	1.2 (0.8-1.9)
	III	103	160	1.4 (1.0-2.0)	1.0 (0.6-1.7)
	IV	139	162	1.8 (1.3-2.6)	1.1 (0.6-2.1)

*Adjusted for age, sex, cigarette smoking, and BMI.
†Adjusted for age, sex, cigarette smoking, BMI, and dietary caloric intake.

1.5 (95% CI = 1.0-2.2), respectively. Risks for the corresponding quartiles of plant protein intake were 1.0 (95% CI = 0.7-1.5), 1.1 (95% CI = 0.8-1.7), and 1.3 (95% CI = 0.9-2.0), respectively. After caloric adjustment, however, risks for animal or plant protein were reduced to near unity (Table 2). This phenomenon may be explained, in part, by the inverse correlations between animal and plant proteins within the second and third quartiles of caloric intake. The Pearson correlation coefficients within each quartile of caloric intake were .14, –.34, –.27, and .25.

The association between renal cell cancer and amount of protein consumption was similar by level of smoking and quartile of BMI. Further adjustment for other variables, including a history of kidney diseases and hypertension and the use of diuretic or antihypertensive medications, did not alter the association with protein intake.

Nutrient findings for next-of-kin case subjects were consistent with those for directly interviewed patients as a group, particularly for protein intake. The nutrient findings were not changed materially when contributions from supplements or alcohol were added to the dietary intake. Risk was not related to use of dietary supplements. Furthermore, no association was observed for degree of "doneness" (rare, medium-rare, medium, medium-well, or well-done/charred) or method of cooking of red meat (baked/roasted, fried/sautéed, boiled/stewed, or broiled/grilled). Beverages such as coffee, tea, and alcoholic drinks were not related to risk of renal cell cancer.

Table 3. ORs* and 95% CIs for renal cell cancer in relation to protein and calorie consumption among Minnesota residents

	Protein quartile							
	I (low)		II		III		IV (high)	
Calorie quartile	OR (95% CI)	No. of direct cases/controls	OR (95% CI)	No. of direct cases/controls	OR (95% CI)	No. of direct cases/controls	OR (95% CI)	No. of direct cases/controls
I (low)	1.0 (—)	57/123	1.1 (0.6-2.2)	17/34	0.5 (0.0-4.6)	1/4	— (—)	0/0
II	0.8 (0.4-1.6)	12/35	1.2 (0.7-2.0)	46/86	1.0 (0.6-2.0)	19/40	---- (----)	0/2
III	1.2 (0.1-14.6)	1/2	1.0 (0.5-1.9)	19/39	1.6 (1.0-2.6)	69/90	2.2 (1.2-3.9)	35/33
IV (high)	— (—)	0/1	0.9 (0.2-5.1)	2/5	1.6 (0.9-3.2)	21/29	1.9 (1.3-2.9)	116/127
Total protein†	1.0 (—)		1.2 (0.7-1.9)		1.4 (0.8-2.5)		1.9 (1.0-3.6)	

*Adjusted for age, sex, cigarette smoking, and BMI.
†Also adjusted for caloric intake.

Table 4. ORs* and 95% CIs for renal cell cancer in relation to protein and fat consumption among Minnesota residents

	Protein quartile								
	I (low)		II		III		IV (high)		Total fat†
Fat quartile	OR (95% CI)	No. of direct cases/controls	OR (95% CI)	No. of direct cases/controls	OR (95% CI)	No. of direct cases/controls	OR (95% CI)	No. of direct cases/controls	OR (95%CI)
I (low)	1.0 (—)	56/111	1.1 (0.6-2.0)	21/42	2.3 (0.7-7.7)	6/6	3.3 (0.7-15.5)	4/3	1.0 (---)
II	0.5 (0.2-1.0)	11/44	1.0 (0.6-1.6)	34/70	1.0 (0.5-1.9)	22/43	2.4 (0.7-8.3)	6/5	0.7 (0.4-1.0)
III	1.1 (0.3-4.5)	3/6	1.2 (0.7-2.1)	28/45	1.6 (1.0-2.5)	64/77	2.3 (1.3-4.0)	41/36	0.9 (0.6-1.4)
IV (high)	— (—)	0/0	0.3 (0.0-2.5)	1/7	1.0 (0.5-1.9)	18/37	1.5 (1.0-2.4)	100/118	0.6 (0.3-1.0)
Total protein‡	1.0 (—)		1.3 (0.9-2.1)		1.8 (1.1-3.0)		2.9 (1.7-5.1)		

*Adjusted for age, sex, cigarette smoking, and BMI.
†Also adjusted for protein intake.
‡Also adjusted for fat intake.

Discussion

Since the 1970s, when the first reports of correlations between kidney cancer mortality and per-capita consumption of protein and fat were published (*5,6*), the role of diet in kidney cancer risk has been examined in a number of case–control studies (*20-28*). Elevated risks with high intake of meat, poultry, fish, and milk have been observed in several studies, although only a few studies reported statistically significant associations with consumption of meat (*21,24,27*) or milk (*23,24*). Few previous investigations of renal cell cancer have examined associations with nutrient components from combined food sources. In one case–control study (*24*), increased risk of renal cell cancer was linked to the amount of animal protein consumption, even after adjustment for caloric intake.

In our large population-based, case–control study, several food groups composed of items high in protein were significant risk factors. Furthermore, analyses of nutrient intake suggested that the most likely dietary risk factor was protein. Risk increased with protein consumption independent of calories, particularly when caloric consumption was above the median intake (quartiles III and IV). Because consumption of fat and protein was strongly correlated, we attempted to separate the risks associated with each of these components by cross-classifying quartiles of fat and protein intake. Within levels of fat intake, risk of renal cell cancer tended to increase with protein consumption, with no evidence of rising risks for fat consumption within levels of protein intake. When we attempted to partition the effect of macronutrients that constitute caloric intake by including fat, protein, and carbohydrate in a single model, similar increases in risk were associated with the amount of protein intake. This finding is evidence against a general energy effect, since no increases were found for fat and carbohydrate (*17*). We also found that the effect of protein was not explained by the major risk factors for renal cell cancer, i.e., smoking and high BMI. Conversely, although protein intake and body mass index were weakly correlated, protein intake accounted for only a small part of the association between excess weight and renal cell cancer risk. These results suggest that protein intake plays a role in renal cell cancer risk, regardless of the type or amount of consumption of other macronutrients or calories. However, given the statistical difficulties in separating the effects among individual macronutrients and caloric intake, we recognize that other dietary and nutritional explanations of our findings are possible.

In our data, the risk of renal cell cancer was associated with the overall estimate of protein intake, whether the sources of protein were plant or animal. This finding was consistent with analyses of food groups, suggesting that the combined protein intake, regardless of source, rather than any particular food group was linked to risk. The results differ somewhat from another investigation of renal cell cancer that implicated animal protein, but not plant protein (*24*). We observed an apparent anomaly, however, when adjustment for calories eliminated the separate effects of animal and plant proteins, but not total proteins. The reason for this discrepancy is not clear, although an inverse correlation between animal and plant protein consumption was observed in the second and third quartiles of caloric intake in our data. This inverse pattern by type of protein may explain, in part, the lack of association with either animal or plant protein individually when adjustment was made for calories in a regression model.

It is noteworthy that, in animal models, high protein intake has been shown to induce glomerular and tubular hypertrophy (*29*) and to promote renal damage and functional changes that may enhance the susceptibility of tubular cells to nephrotoxic or carcinogenic exposure (*30,31*). In humans, protein reduction has been shown to slow the progression of chronic renal insufficiency and diseases such as nephrotic syndrome (*32-34*).

The relation of protein intake to kidney disease and function is interesting in view of the increased risk of renal cell cancer among patients with a history of kidney stones, cystic disease, urinary tract infection, hypertension, and other renal diseases (*21,25,28,35-38*), although the associations may be related in part to medications such as diuretics (*4*). Since most of the investigations were case–control studies, recall bias for previous kidney diseases cannot be ruled out, and the pre-existing conditions were generally based on small numbers. In a mortality follow-up study of nearly 34 000 university alumni (*39*), the risk of kidney cancer increased over threefold (relative risk = 3.3; 95% CI = 1.1-9.5) among men who had proteinuria as determined during a routine medical examination at the time of college entrance decades earlier. Although the mechanisms are unclear, certain nonmalignant kidney disorders may be an intermediate stage between high intake of protein and renal cell cancer. However, in our study, adjustment for a history of kidney disease did not alter the association with protein intake, although some renal conditions could have gone unnoticed and under-reported. On the other hand, a direct role for dietary protein or constituent amino acids is possible in view of experimental evidence that suggests a promoting effect on chemically induced tumors and preneoplastic lesions of the liver and breast (*40,41*).

We were unable to confirm several dietary factors previously associated with renal cell cancer, including the elevated risk associated with margarine and oil intake (*25*) and the reduced risks associated with consumption of vegetables (*24,27*) and fruit (*27*). The lack of association with preserved meat in our study suggests that intake of nitrites and nitrates may not be an important risk factor for renal cell cancer, despite experimental evidence that nitrosamines can induce renal carcinomas (*42*). In addition, we found no relation to the method of cooking meat or the degree of "doneness" that would support the hypothesis that the protein association may be due to pyrolysis products, such as heterocyclic aromatic amines (*24*). Consistent with most previous studies, we observed no association with consumption of coffee, tea, or alcoholic beverages (*4*).

Some limitations of the study should be noted. The relatively moderate number of dietary items (65 items) included in the questionnaire might have reduced the chance of detecting an effect for some nutrients. Nevertheless, nutrients estimated from the short version of the Block questionnaire (*43*) used in our study correlated strongly with those estimated from the longer version and with dietary records of food intake. In addition, dietary information was not obtained from about 20% of patients and control subjects. To the extent that dietary patterns for nonrespondents may differ from those who participated in the study, the current study results cannot be generalized to nonrespondents. Because of the relatively poor survival from renal cell cancer, dietary information for more than 20% of the study case patients was provided by their next of kin. Separate analyses for next-of-kin case subjects and directly interviewed patients, however, showed consistent findings, suggesting that these results are not likely due to survival bias.

In summary, our case–control study of renal cell cancer suggests an etiologic role for dietary protein, which warrants continued evaluation in epidemiologic and experimental studies. Such studies should help to further distinguish the effects of protein intake from those of calories and fat, the role of specific proteins and amino acid components, the factors underlying the relation of high body mass index to renal cell cancer, and the possible relation of dietary protein to precursor lesions of the kidney.

Appendix Table 1. Compositions of food groups

Food group	Composition
Red meat	Hamburgers/meatloaf, beef steaks/roasts, ham/lunch meats, pork chops/roasts, spaghetti/lasagna/pasta, beef stew/pot pie, hot dogs, liver/chicken livers
Chicken/fish	Chicken/turkey, fried chicken, fried fish/fish sandwich, other fish (broiled/baked)
Preserved meats	Ham/lunch meats, bacon, sausage, hot dogs
All meats	All of the above combined
Dairy	Whole milk, 2% milk, skim/1%/buttermilk, milk/cream in coffee/tea, milk on cereals, cheese, cottage cheese, ice cream, pizza
Citrus fruit/juices	Orange, grapefruit, orange/grapefruit juice
All fruits	Orange, grapefruit, orange/grapefruit juice, bananas, apple/applesauce/pears, canteloupe, other fruits/grapes/cocktail, other fruit juices
Yellow/green vegetables	Broccoli, spinach, sweet potatoes/yam, carrots, mixed vegetables with carrots, mustard/collard/turnip greens
Cruciferous vegetables	Broccoli, cole slaw/cabbage/sauerkraut, mustard/collard/turnip greens
All vegetables	Green salad, carrots/mixed vegetables with carrots, tomatoes/tomato juice, beans/pintos/kidney/limas, broccoli, cole slaw/cabbage/sauerkraut, spinach, mustard/collard/turnip greens, other vegetables/green beans/corn/peas
Staple foods	White bread/cracker/bagel, dark bread/whole wheat/rye, biscuits/muffins/rolls, corn bread/muffin/tortilla, high fortified cereals, bran/granola cereal, other cold cereals, cooked cereals, french fries/fried potatoes, other potatoes, rice, spaghetti/lasagna/pasta
Desserts	Doughnuts/cookies/cakes, pies, ice cream, chocolate candies
High-protein foods	Whole milk, 2% milk, skim/1%/buttermilk, eggs, cheese and cheese spread, hamburger/meatloaf, beef steaks/roasts, pork chops/roasts, chicken/turkey, fried chicken, spaghetti/lasagna/pasta, beef stew/pot pie, fried fish/fish sandwich, other fish, liver/chicken liver
Restaurant foods and fast foods	Hamburgers, pizza, fried chicken, fried fish, Chinese food, Mexican food, other restaurant foods/fast foods

Appendix Table 2. Cutpoints for quartiles of servings of food group per week (by sex)

Food group	Sex	Quartiles			
		I (low)	II	III	IV (high)
Red meat	Male	≤4.3	4.4-6.3	6.4-9.1	≥9.3
	Female	≤3.8	3.9-5.8	5.9-8.4	≥8.5
Chicken/fish	Male	≤1.0	1.1-1.8	2.0-2.8	≥3.0
	Female	≤1.1	1.2-1.8	2.0-2.8	≥3.0
Preserved meats	Male	≤1.4	1.5-2.8	2.9-4.9	≥5.0
	Female	≤1.0	1.1-2.1	2.3-3.9	≥4.0
All meats	Male	≤7.0	7.1-9.6	9.8-12.6	≥12.8
	Female	≤6.3	6.4-8.5	8.6-12.4	≥12.5
Dairy	Male	≤9.6	9.7-16.5	16.6-28.9	≥29.0
	Female	≤8.7	8.8-15.2	15.3-26.6	≥26.8
Citrus fruit/juices	Male	≤1.1	1.3-3.8	4.0-.71	≥7.3
	Female	≤2.0	2.3-5.1	5.5-8.6	≥9.0
All fruits	Male	≤4.3	4.5-7.8	7.9-11.8	≥11.9
	Female	≤6.1	6.2-10.0	10.3-15.1	≥15.2
Yellow/green vegetables	Male	≤0.8	0.9-1.5	1.6-2.5	≥2.6
	Female	≤1.0	1.1-2.0	2.1-3.8	≥3.9
Cruciferous vegetables	Male	≤0.3	0.5-0.8	0.9-1.3	≥1.5
	Female	≤0.5	0.6-0.9	1.0-1.6	≥1.9
All vegetables	Male	≤5.1	5.3-8.0	8.1-12.3	≥12.4
	Female	≤7.3	7.4-10.1	10.3-14.0	≥14.1
Staple foods	Male	≤13.0	13.1-18.8	18.9-24.3	≥24.5
	Female	≤13.8	14.0-19.0	19.1-25.8	≥26.1
Desserts	Male	≤2.6	2.8-5.8	6.0-9.3	≥9.5
	Female	≤2.1	2.3-5.6	5.8-8.9	≥9.0
High-protein foods	Male	≤12.4	12.5-18.1	18.5-27.0	≥27.1
	Female	≤11.6	11.8-16.4	16.5-24.8	≥25.6
Restaurant foods and fast foods	Male	≤0.5	0.6-1.1	1.2-2.2	≥2.2
	Female	≤0.4	0.4-0.9	1.0-1.7	≥1.8

Appendix Table 3. Cutpoints for quartiles of nutrient intake per day (by sex)

Nutrient (unit)	Sex	Quartile			
		I (low)	II	III	IV (high)
Calorie (kcal)	Male	≤1188.8	1191.1-1570.6	1571.7-2024.4	≥2025.4
	Female	≤1067.7	1072.0-1368.6	1370.7-1810.4	≥1812.7
Carbohydrates (g)	Male	≤121.1	122.0-169.9	170.3-220.2	≥220.4
	Female	≤115.9	116.2-148.8	149.9-198.6	≥199.0
Total proteins (g)	Male	≤49.1	49.2-66.5	66.6-87.4	≥87.5
	Female	≤43.5	43.7-55.0	55.3-72.2	≥72.3
Animal protein (g)	Male	≤32.4	32.5-44.9	45.1-62.3	≥62.6
	Female	≤26.9	27.0-37.4	37.5-50.8	≥51.0
Plant protein (g)	Male	≤15.0	15.1-20.8	20.9-27.2	≥27.3
	Female	≤14.1	14.2-18.3	18.4-24.3	≥24.4
Total fat (g)	Male	≤51.2	51.3-69.9	70.0-94.4	≥95.2
	Female	≤44.5	44.8-60.5	60.6-84.1	≥84.9
Saturated fat (g)	Male	≤17.9	18.0-25.6	25.7-33.9	≥34.0
	Female	≤15.2	15.5-20.8	21.0-29.6	≥29.7
Beta carotene (μg)	Male	≤944.5	948.4-1436.4	1464.4-2338.3	≥2400.8
	Female	≤829.9	839.2-1606.4	1608.3-2503.6	≥2528.1
Vitamin C (mg)	Male	≤54.9	55.0-83.4	83.7-126.8	≥128.1
	Female	≤67.6	68.3-96.6	97.1-134.6	≥137.6
Vitamin E (TE)*	Male	≤5.3	5.4-7.4	7.5-10.1	≥10.2
	Female	≤5.3	5.4-7.0	7.1-9.5	≥9.6
Calcium (mg)	Male	≤441.2	442.8-691.8	694.4-1097.6	≥1098.7
	Female	≤382.8	383.0-576.6	578.4-872.5	≥885.4
Iron (mg)	Male	≤7.9	8.0-10.6	10.7-13.6	≥13.7
	Female	≤6.7	6.8-9.4	9.5-11.8	≥12.0

*TE = milligrams of alpha tocopherol equivalent (1 TE = 1.5 IU).

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Note

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